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CHAPTER 89
Gestational Diabetes Mellitus

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Hyperglycemia first identified during pregnancy has been accepted as the arbitrary definition of gestational diabetes mellitus (GDM). The adverse effects of glycosuria and carbohydrate intolerance in pregnancy on fetal outcome were described nearly 100 years ago (1). Subsequently, in 1917, Elliot P. Joslin (2) described Case 309, which "showed sugar in 1897 during pregnancy, but following confinement, with resulting dead baby, it disappeared, but returned in 9 years in the form of moderate to severe diabetes.... [W]ith our present knowledge it is quite possible that such an outcome could be prevented by active treatment of the glycosuria from the very start" (2). Joslin's description emphasizes the importance that the identification of GDM has on perinatal morbidity and mortality, as well as subsequent development of diabetes mellitus (DM) in the mother. The differential effects on the mother and child have caused some dilemmas in both the ultimate diagnosis of the disorder and the aggressiveness with which it is sought and treated.

Gestational DM may be viewed as:

1. An unidentified preexisting disease, or
2. The unmasking of a compensated metabolic abnormality by the added stress of pregnancy, or
3. A direct consequence of the altered maternal metabolism stemming from the changing hormonal milieu.

Based on a statistical analysis of the Second National Health and Nutritional Examination and Survey (NHANES II), Harris (3) questioned the uniqueness of GDM. Glucose tolerance testing of 817 nonpregnant women of childbearing age with no previous history of DM found prevalence rates of carbohydrate intolerance virtually identical to those described in pregnancy. A substantial number of women identified as diabetic during pregnancy, therefore, could have been identified by the improved ascertainment arising from closer monitoring, as recommended during pregnancy. This is further suggested by the findings that those diagnosed with GDM before 24 weeks' gestation were significantly older and had a twofold greater incidence of required insulin therapy than did women diagnosed after 24 weeks' gestation (4).

This controversial position can be refuted, at least partially, by the observation that most subjects with GDM revert to normal carbohydrate tolerance postpartum. Another limitation of the conclusion is the fact that Harris used glycemic parameters developed for the diagnosis of GDM, but in a nonpregnant population. Although the level of glycemia achieved by the two groups is comparable, neither the metabolic milieu nor the potential complications are the same. If traditional diagnostic criteria for DM in nonpregnant adults are applied to the population studied by NHANES II, the prevalence of DM is considerably less. The critical point remains, however, that a substantial subset of women diagnosed with GDM, particularly those diagnosed early in pregnancy, may have had preexisting disease that had gone undiagnosed. The apparent clinical correlate of this finding is the need to assess fasting glucose concentrations at the beginning of pregnancy in order to diagnose preexisting carbohydrate intolerance.

A second possibility is that pregnancy creates a metabolic stress that simply pushes a woman with compensated type 1 DM or type 2 DM into a decompensated hyperglycemic state. It is clear from the classic studies of Freinkel et al. (5) that insulin requirements rise substantially during normal pregnancy. If a woman has a limited β-cell response secondary to autoimmune β-cell destruction, as seen in type 1 DM, or has β-cell secretory reserve insufficient to meet the demands of pregnancy because of early type 2 DM, she may decompensate from a normoglycemic state in the nonpregnant situation to a hyperglycemic state during pregnancy. Data supporting the hypothesis that pregnancy results in the decompensation of a prediabetic stage of type 1 DM include a twofold enrichment in the frequency of human leukocyte antigens DR3 and DR4 in women with GDM compared with that of a racially matched, carbohydrate-tolerant pregnant population (6), and the finding of islet cell antibodies in as many of 31% of women in whom GDM developed (7). In addition, in 20% of women with previous GDM in whom DM subsequently develops, traditional type 1 DM develops, as defined by a deficient C-peptide response to intravenous

glucose (8). Others have been less successful in finding evidence of autoimmunity in women with GDM, suggesting that fewer than 10% may have incipient type 1 DM (9).

It is far more likely that GDM results from decompensation of a prediabetic stage of type 2 DM. Pathophysiologic observations of GDM are very similar to those seen in type 2 DM and are discussed in detail later in this chapter. Epidemiologically, however, most people in whom DM develops after a history of GDM have classic type 2 DM. Review of 12 worldwide studies of DM among former patients with GDM indicates a wide range of incidence rates, from 19% to 87% for combined DM and impaired glucose tolerance, to 6% to 62% for DM alone (10). Depending on the ethnic group, conversion rates postpartum to nongestational DM may be as high as 9% within the first 6 weeks (11), with 30% in the first year (12). The initial observations of O'Sullivan and Mahan (13) in 752 unselected pregnant women in the 1960s demonstrated a 50% prevalence of DM after 28 years of follow-up in those in whom pregnancy was complicated by GDM. In addition, as is shown subsequently, the prevalence of GDM parallels the prevalence of type 2 DM in high-risk ethnic and racial groups.

HOW IS GESTATIONAL DIABETES MELLITUS DEFINED?

The National Diabetes Data Group (NDDG), together with the first three International Gestational Diabetes Workshops, accepted the modified criteria originally described by O'Sullivan and Mahan (13) in their classic study of 1964. A statistical analysis of glucose response over 3 hours to a 100-g oral glucose challenge in 752 healthy, pregnant women yielded values representing the mean plus or minus two standard deviations in the fasting state and at 1, 2, and 3 hours. By arbitrarily declaring abnormal carbohydrate handling as that exceeding two standard deviations above the mean on two or more values, 2.5% of the population was defined as having GDM. This statistical means of defining disease is population specific, with a prevalence of GDM ranging from 0.5% in northern England to 12.3% in the inner-city (predominantly Hispanic and African-American) population (14). With a mixed inner-city African-American and tertiary care population, the George Washington University Medical Center has a 4% prevalence of GDM in its obstetric practice. In a review of an ethnically diverse cohort of 10,187 women undergoing standardized screening for glucose intolerance in New York City, the overall prevalence of GDM was 3.2%. The frequency of GDM was lowest for whites, followed by African Americans, Hispanics, Asians, and women classified as belonging to another "racial/ethnic group" (14). Thus, the purely statistical approach to the definition of GDM is inappropriate because it depends on the relative risk of the populations studied.

A more suitable method of defining disease is based on the morbidity associated with the condition. The O'Sullivan-Mahan criteria have stood the test of time as a predictor of subsequent DM in the mother, as previously mentioned. Perinatal maternal morbidity is likewise reflected in the significantly increased incidence of pregnancy-induced hypertension and preeclampsia (15). With current aggressive glycemic management achieving postprandial euglycemia, the traditional maternal complications of polyhydramnios, preterm labor, abnormalities of labor, and birth trauma are not increased in this population with GDM. The predominant acute effects of GDM occur not to the mother but to the fetus.

Neonatal morbidity in the offspring of women with GDM has long been recognized. The occurrence of metabolic complications, including hypoglycemia, hypocalcemia, macrosomia, and hyperbilirubinemia, is excessive (16). With improved neonatal care, it is difficult to demonstrate changes in fetal mortality rates. Older data, however, did report a fourfold increased mortality rate in infants of mothers with GDM (17). The effects on the offspring are not limited, however, to the immediate perinatal period. As these offspring of mothers with GDM age, they acquire premature insulin resistance, obesity, and a high rate of carbohydrate intolerance (18).

It would appear, therefore, that diagnosing GDM and instituting aggressive management of the mother are intended to reduce or eliminate the perinatal, neonatal, and long-term complications in the offspring. The current diagnostic criteria, however, in no way take the neonatal outcome into consideration. With this in mind, are the O'Sullivan-Mahan criteria too lax for the identification of people at risk for perinatal morbidity associated with carbohydrate intolerance? The sanctity of these criteria has been seriously questioned (19). The original criteria were based on whole-blood determination of glucose by the Somogyi technique. This was subsequently modified by the NDDG to use a conversion factor of 1.14 to represent plasma glucose determinations by the glucokinase technique (20). Technical modifications of that conversion have been recommended by Carpenter and Coustan (21) as being more representative of the true plasma glucose determination. This modification results in a lowering of all glucose criteria in the 3-hour glucose tolerance test (Table 89-1). As such, a larger percentage of women undergoing glucose tolerance testing during pregnancy will meet these modified criteria, thus increasing the sensitivity of the test; however, the effects of these more inclusive criteria on specificity remain in doubt (22). By using the lower modified criteria, the overall incidence of GDM increased by 56%. Data on the modified criteria presented at the Fourth International Workshop on Gestational Diabetes indicated that infants of women meeting these lower criteria are at a risk for perinatal morbidity, including macrosomia, similar to that of those patients identified using NDDG criteria (23). Therefore, the Carpenter and Coustan criteria were adopted for diagnosis (23). Long-term follow-up of this patient population is not yet available.

The Fourth International Workshop on Gestational Diabetes defined cut-off values for the controversial 75-g oral glucose

TABLE 89-1. Historical evolution of O'Sullivan-Mahan criteria for the diagnosis of gestational diabetes mellitus

	O'Sullivan-Mahan criteria [mM (mg/dL) whole blood]	National Diabetes Data Group criteria [mM (mg/dL) plasma]	Carpenter-Coustan modification [mM (mg/dL) plasma]
Fasting	5.0 (90)	5.83 (105)	5.28 (95)
1 hr	9.17 (165)	10.56 (190)	10.0 (180)
2 hr	8.06 (145)	9.17 (165)	8.61 (155)
3 hr	6.94 (125)	8.06 (145)	7.78 (140)

Adapted with permission from ref. 39.

erance test (GTT) in pregnancy. This test, used in Europe for many years, had no standard criteria. Because outcomes data are unavailable, the cut-off values were arbitrarily defined based on the mean plus 1.5 standard deviations of the OGTT values in a study of over 3,500 patients (24) (Table 89-2). Despite the disparate glucose challenge, the 2-hour value was raised to 155 mg/dL to be more consistent with the 2-hour value recommended for the 100-g OGTT and the values for the European Association for the Study of Diabetes (25). Studies suggest that lowering the glucose values to a fasting value of 90 mg/dL and a 2-hour value of 140 mg/dL, closer to the current World Health Organization criteria (26); should be considered to reduce significantly the rate of large-for-gestational-age infants and obstetric interventions (27) (Table 89-3). Greater experience in use of the 75-g OGTT and maternal and infant outcomes data will be needed to define better the cut-off values for this test.

In addition to the debate concerning the appropriate glucose tolerance test criteria for use in the diagnosis of GDM, data are becoming increasingly available to suggest that a single abnormal value on glucose tolerance testing may better predict the occurrence of perinatal morbidity. Tallerigo et al. (29) examined the neonatal outcome in 249 women with normal glucose tolerance test results in the third trimester by the O'Sullivan-Mahan criteria. They found that the 2-hour plasma glucose concentration after a 100-g OGTT significantly correlated with the infant's birth weight: the higher the 2-hour plasma glucose concentration, the greater the incidence of macrosomia, toxemia, and cesarean sections. A significant increase was noted as 2-hour plasma glucose concentrations exceeded 140 mg/dL compared with the 165 mg/dL cut-off noted in the traditional O'Sullivan-Mahan criteria. Others have correlated the rate of fall in plasma glucose concentration in the first hour after an intravenous glucose tolerance test with neonatal complications. Decreased glucose disposal, as manifested by a slower rate of decline in plasma glucose, correlated with increased infant birth weight, neonatal asphyxia, and congenital anomalies (30). Validation of these findings has been provided by additional large-scale epidemiologic studies. Lindsay et al. (31) found both maternal and fetal morbidity increased in women with only a single abnormal value on glucose tolerance testing during pregnancy. Toxemia was increased in the affected group with an odds ratio of 2.51, and macrosomia and subsequent shoulder dystocia in the infants were found to have odds ratios of 2.18 and 2.97, respectively. In mothers with only a single abnormal value on glucose tolerance testing, Berkus and Langer (32) found the incidence of infants who were large for gestational age to be twice that of mothers in whom the glucose tolerance test was entirely normal. Intervention to maintain normoglycemia during pregnancy reduced this adverse outcome to near-normal levels.

Finally, reservations about the OGTT as a means of diagnosis have been raised, regardless of the criteria used. Poor reproducibility of glucose tolerance testing has been documented since the early 1940s (33). This issue has been examined in a study during pregnancy, in which high-risk pregnant women underwent two sequential glucose tolerance tests 1 week apart; 24% had discrepant test results on the two examinations (34). Progression from normal to abnormal values due to progressive decompensation could not explain this inconsistency, because 80% of the discrepant test results reverted from abnormal to normal at the second examination.

Because of lack of reproducibility of the glucose tolerance test, together with the discrepancies in the number of abnormalities and the threshold for defining those abnormalities, much effort has gone into establishing simpler diagnostic criteria for GDM. Glycated proteins are extensively used to follow long-term levels of glycemic control. Many have hoped to adapt this simple blood test, which can be obtained without dietary preparation and at any time of day, as a diagnostic test for GDM. Unfortunately, neither glycated hemoglobin nor fructosamine is sufficiently sensitive for the identification of women with GDM (35–37). Random glucose testing and use of reflectance meters lack the sensitivity for adequate identification of women at risk for GDM. The best screening test appears to be the 50-g 1-hour glucose challenge test. It is now recognized that a 50-g oral glucose load can be used in either the fasting or the fed state without reducing sensitivity or specificity (38). A screening threshold of 130 mg/dL provides a sensitivity approaching 100% while maintaining specificity at near 80% (39). Alteration of this threshold for subsequent 3-hour 100-g glucose tolerance testing influences the sensitivity, specificity, and ultimate cost of universal screening. Universal screening of all pregnant women using a threshold value of 130 mg/dL results in an almost 100% sensitivity at a cost of $249 per case diagnosed. Screening limited to women older than 25 years of age, or to younger women with risk factors, maintains the sensitivity at more than 95%, but with only a $35 reduction in cost per case diagnosed (40).

The Second International Workshop conference on GDM concluded that all pregnant women should be screened for GDM (41). A 1-hour plasma glucose determination in excess of 140 mg/dL (lower by Carpenter-Coustan criteria) constitutes a positive screen and requires the performance of a traditional 100-g OGTT for confirmation of GDM. Selective screening based on clinical and obstetric history has previously been deemed inadequate. However, large studies suggest that the efficiency of screening improves by assessing only women at high risk (42,43). Naylor et al. (42) evaluated data on over 3,000 pregnant women and developed a scoring system to determine risk of GDM. Scores are based on age, body mass index (BMI), and race. They rationalized that those with low scores need not be evaluated, which allows one third of women to avoid the glucose challenge test (42). They also suggested that those with high scores should have a lower cut-off value on their glucose challenge test. Currently accepted clinical management

TABLE 89-2. Mean glucose values for 75-g glucose tolerance test during pregnancy

	Sacks et al. (24)		Moses et al. (27)	
	mg/dL ± SD	mmol/L ± SD	mg/dL ± SD	mmol/L ± SD
Fasting	83.6 ± 8.9	4.6 ± 4.9	76.9 ± 8.3	4.27 ± 0.46
1 hr	124.4 ± 32.9	6.9 ± 1.83	104.0 ± 32.0	5.78 ± 1.78
2 hr	108.4 ± 24.8	6.0 ± 1.38		

TABLE 89-3. Criteria for diagnosis of gestational diabetes mellitus with a 75-g oral glucose load [mg/dL (mmol/L)]

	WHO (26)	European Association for Study of Diabetes (25)	Fourth International Workshop on GDM[a] (23)	Australia (28)	Moses et al. (27)
Fasting	Unfavored	—	95 (5.3)	99 (5.5)	90 (5.0)
1 hr	—	—	180 (10.0)	—	—
2 hr	140 (7.8)	162 (9.0)	155 (8.6)	144 (8.0)	140 (7.8)

GDM, gestational diabetes mellitus; WHO, World Health Organization.
[a]Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be performed in the morning after an 8- to 14-hour fast and after at least 3 days of unrestricted diet and physical activity.

includes screening for GDM between gestational weeks 24 and 28 in pregnant women older than 25 years of age who have not been previously identified as having glucose intolerance. The recent American Diabetes Association position statement suggests that it is not cost effective to screen women at low risk (i.e., age < 25 years, ethnic groups at low risk for type 2 DM, no history of abnormal glucose tolerance, normal body weight, and no family history of DM) (23). This new policy has been controversial, however, with some suggesting that 10% of patients with GDM would be missed if all women were not screened (44).

Glucose traditionally has been used as the marker for GDM because of its ease of measurement and test reproducibility among laboratories. It is now clear that alterations in insulin secretion, insulin sensitivity, and carbohydrate, fat, and amino acid metabolism are all intrinsic abnormalities in the state that we have come to accept as GDM. Developing more sensitive indices for prediction of perinatal morbidity may require either intensification of glycemic criteria or the inclusion of more sophisticated metabolic measurements.

ETIOLOGY AND PATHOGENESIS OF GESTATIONAL DIABETES MELLITUS

Epidemiologically, GDM has much in common with type 2 DM. Like type 2 DM, the frequency of GDM increases with progressive age and body mass index and is seen more commonly in nonwhite populations. In various studies, the relative risk is increased by 1.6 to 3.5 in African Americans, 1.8 in Hispanics, 8.5 in Southeast Asians, 10.9 in East Indians, and 15 in Native Americans (45,46). These findings parallel those of type 2 DM in these respective ethnic groups, as well as in relation to age and obesity. Metabolic assessment of women with previous histories of GDM further reveals findings consistent with type 2 DM. In addition to the observation that over 90% of women in whom nongestational DM develops after a history of GDM appear to have type 2 DM (47), metabolic studies suggest both β-cell defects and insulin resistance in women with a history of GDM.

It is useful, therefore, to examine the pathogenesis of GDM by examining the β-cell insulin response and subsequent insulin action in pregnant women both with and without GDM. Classic studies by Freinkel (48) and others demonstrated a 1.5- to 2.5-fold augmentation in insulin secretion in response to either oral or intravenous glucose during pregnancy. Clearly, limited β-cell reserve incapable of making this compensatory increase in insulin secretion would result in subsequent maternal carbohydrate intolerance. After an oral glucose challenge to women with GDM, significantly higher insulin levels are reached in pregnancy than are seen in the same women postpartum (48).

In absolute terms, women with GDM have insulin responses almost identical to those of normal women during pregnancy (49). Because the ambient glucose levels are higher in GDM, however, the insulin response per unit of glycemic stimulus (the insulinogenic index) is only half that seen in normal pregnancy.

Specific stimulation tests have revealed enhanced β-cell sensitivity to both glucose and amino acids in normal pregnancy. These responses, however, are significantly lower in women with GDM (50). β-cell secretory dynamics may be assessed by intravenous glucose tolerance testing and analyzed by minimal modeling techniques (51). First-phase insulin secretion was less than one-fourth that of the normal pregnant group (52). In the second phase, insulin secretion was also found to be lower in the women with GDM, although not sufficiently so to reach statistical significance. In this group of 16 women with GDM, however, only 1 was found to have both normal first- and second-phase insulin secretion. These findings are entirely consistent with observations of β-cell response and dynamics in nongestational type 2 DM (53). It remains unclear whether this β-cell defect is present before conception. No prospective studies before the occurrence of GDM have been published to demonstrate this proposed preexisting β-cell defect. It is clear, however, that the β-cell defect persists after delivery. Oral glucose tolerance testing in women with previous GDM matched with women with a history of normal pregnancy demonstrates a 25% to 40% reduction in insulin responsiveness in both white and African-Caribbean patients. The insulin : glucose ratios are also reduced by 30% to 45% in these populations (54).

As in type 2 DM, it is not known whether the β-cell defect seen in GDM is a primary defect or occurs after insulin resistance. Nonetheless, insulin resistance is a well described phenomenon in GDM. Using techniques similar to those in type 2 DM, insulin sensitivity is found to be markedly depressed in GDM and glucose disposal rates are markedly diminished. Using a hyperinsulinemic euglycemic clamp technique, Ryan et al. (55) demonstrated insulin resistance in women with normal pregnancies and GDM, with glucose utilization decreasing by 18% and 58%, respectively, compared with normal, nonpregnant women. Using the minimal model technique, however, insulin sensitivity was reduced by two thirds in both normal pregnant women and those with GDM compared with matched, nonpregnant women. Thus, no differences were noted by this method in insulin action in GDM versus normal pregnancy (52).

Examination of insulin action on peripheral tissues, specifically liver, adipocyte, and muscle, suggests normal insulin action in the two former sites and marked insulin resistance in the muscle. Phosphofructokinase and pyruvate kinase are significantly lower in muscle tissue from pregnant women compared with nonpregnant control subjects (50). This results in decreased muscle glycolysis and glucose disposal, and may be related to increased free fatty acids (FFA) during pregnancy. FFA, which stimulate fat oxidation and decrease carbohydrate oxidation, rise during late pregnancy. When FFA are artificially increased in early gestation, at which time insulin sensitivity

normal, insulin-stimulated glucose uptake decreases by 30% (56). This insulin resistance is less than that found during late pregnancy, accounting for only part of the insulin resistance in GDM.

These changes in insulin sensitivity are found inconsistently postpartum. Ryan et al. (55) found normal glucose disposal 3 days postpartum in two patients with a history of GDM. With larger samples, however, only 50% of women with previous GDM normalized their insulin sensitivity and glucose disposal (57,58).

Like type 2 DM, GDM is a genetically heterogeneous disorder. Clear ethnic differences in both phenotypic and genotypic features exist. In both African-American and white subjects, the presence of genotypes 1,1 and 1,2 for the insulin receptor gene increase the relative risk for development of GDM (59). These genotypic markers further interact with both BMI and a maternal history of DM. The presence of allele 1 of the insulin receptor gene confers an odds ratio of 3.72 when the BMI is 35. If a maternal history of DM is factored in, the odds ratio rises to 62.84 (59).

In whites, the interaction between allele 1 positivity in the insulin receptor gene accounts for the entire increased odds ratio related to obesity. Thus, if the BMI is 35 or greater, the odds ratio in allele 1–positive patients rises to 27.4, whereas it is not increased in women lacking the allele. A further interaction occurs between women with allele 1 positivity and insulin-like growth factor-2 allele 2 positivity. This interaction further increases the odds ratio to 34. Hispanic patients in this analysis demonstrated none of the genetic risk factors found in either the white or African-American populations with GDM.

Despite these genetic observations, no definitive abnormalities in insulin receptor number, affinity, or activity have been noted. Available literature demonstrates a wide range of insulin receptor states in GDM. Thus, most investigators believe that the insulin resistance occurring in GDM stems from a postreceptor defect.

Examination of glucose transporter function has provided further evidence of the mechanism of insulin resistance. GLUT-4 content is entirely normal in skeletal muscle in both normal pregnancy and GDM (60). GLUT-4 content in adipocytes, however, is abnormal in both absolute number and subcellular distribution (61). Approximately 50% of patients with GDM have a profound cellular depletion of GLUT-4, whereas the other subgroup demonstrates normal total cellular GLUT-4 with an abnormal subcellular distribution. Insulin-stimulated translocation of GLUT-4 from microsomes into the plasma membrane was markedly deficient in all patients with GDM, with a subsequent 60% depression in glucose transport activity. It is unclear from these studies whether the defect in glucose transporter number, location, or activity is a primary defect present before gestation or if it persists postpartum. It is possible, however, that these defects are acquired as a result of either chronic hyperglycemia or hyperinsulinemia during the period of gestation. Further longitudinal studies of insulin action will be necessary before conclusive evidence is forthcoming.

IMPACT OF GESTATIONAL DIABETES MELLITUS ON THE MOTHER

The identification and treatment of women with GDM are motivated as much by the desire to prevent obstetric complications as by the need to prevent fetal complications. A summary of observational studies revealed increased risks of polyhydramnios, pregnancy-induced hypertension, chronic hypertension, pyelonephritis, and the need for cesarean section delivery (62). Improved obstetric care, and perhaps more intensive management of GDM, result in a reduction to control levels of most maternal complications (63). Pregnancy-induced hypertension and preeclampsia, however, remain twice as common in women with GDM as in normal control subjects. This relationship persists even when matched for maternal BMI. In addition, both chronic hypertension/pregnancy-induced hypertension and preeclampsia are significantly more common (2.5% vs. 1% and 19.8% vs. 7.9%, respectively) in women with GDM compared with BMI-matched women with only a single abnormal value on glucose tolerance testing (64).

Delivery by cesarean section occurs in 13% to 32% of women with GDM, depending on the study (65,66). Highest rates are seen in those women who receive insulin treatment. Despite the increased use of insulin in GDM, cesarean section rates have been declining in the past 15 years (66). This result is presumably due to more strict glycemic control and earlier labor induction, resulting in a decline in the incidence of macrosomia or the number of infants who are large for gestational age. Maternal BMI and nulliparity were the only maternal factors identified that predicted the need for cesarean section. Fetal factors associated with an increased risk of cesarean section included fetal presentation, percentage body fat, and subscapular skinfold thickness (67). The single most common cause of cesarean section among women with GDM, however, remains repeat cesarean section.

Gestational DM recurs in approximately 50% of subsequent pregnancies (68). Additional predictors of recurrent GDM include absolute glucose tolerance test results, glucose response, the requirement of insulin, and the presence of macrosomia in the index pregnancy. Together with a BMI in excess of 35 in the subsequent pregnancy, these three additional risk factors in combination serve as excellent markers for recurrence. The presence of any two factors has an 82% positive predictive value, and the presence of any three carries with it a 100% positive predictive value (69). Today, the O'Sullivan-Mahan criteria remain the only long-term predictors of maternal carbohydrate tolerance. The incidence rates for DM among former patients with GDM varies from 6% to 62%, with an excess risk for DM among these women as high as 31% (10). Extensive efforts to identify factors predicting subsequent maternal nongestational DM have contributed extensively to the understanding of the pathophysiology of GDM. Pregnancy, despite its temporary diabetogenic state, is not associated with an increased risk of subsequent type 2 DM (70).

Preexisting obesity and subsequent postpartum weight gain are strongly associated with the development of type 2 DM (71). Thus, the progression from GDM to type 2 DM appears to be identical to, although faster than, the course of type 2 DM in the non-GDM population. Intensive examination of maternal and neonatal characteristics of a GDM population with postpartum follow-up confirms obesity (or BMI) and the fasting glucose value on the OGTT in pregnancy as the strongest predictors of subsequent development of type 2 DM (72–74). A family history of DM, maternal age, parity, and the need for therapeutic insulin during the index pregnancy were not consistently found to be significant predictors of the ultimate development of type 2 DM.

Gestational DM appears to be an early manifestation of type 2 DM in populations at risk. Early identification allows longitudinal evaluation of metabolic parameters leading to the development of type 2 DM and becomes an excellent model for prevention studies of nongestational DM. GDM has been associated with early atherosclerosis. There is markedly attenuated endothelium-dependent dilatation in patients with GDM compared with control subjects at 3 to 6 months postpartum. This suggests that endothelial dysfunction, an early sign of atherosclerosis, is already present shortly after delivery in women

with a history of GDM, even if they currently have normal glucose tolerance and blood pressure. This may be related to persistent postpartum insulin resistance in these women (75).

IMPACT OF GESTATIONAL DIABETES MELLITUS ON THE FETUS

The fetus of the mother with GDM is exposed to a metabolic milieu quite different from the normal one. Glucose, alanine, and FFA are transferred from the maternal circulation to the fetus in excess quantity, resulting in an overfed fetus (76). As a result, amniotic fluid insulin concentrations rise significantly as an indicator of fetal compensation for increased nutrient delivery (77). Although glucose and glycated proteins, including hemoglobin, become the clearest parameters reflecting the maternal metabolic state, maternal triglyceride concentrations have been found to be the strongest predictor of birth weight (78). Thus, the overall metabolic changes clearly affect fetal development and maturity, leading to a variety of morbid fetal outcomes. Improved maternal and neonatal care has reduced neonatal mortality to levels indistinguishable from those of control groups. The effects of maternal glucose and metabolic control tend to mask the incidence of neonatal complications, but fail to ameliorate them entirely. Population-based studies of perinatal outcomes in patients with GDM reflect an increased prevalence of infants who are large for gestational age, macrosomia, hyperglycemia, hyperbilirubinemia, and polycythemia (79,80). In these studies, triglycerides were not measured, but maternal weight was significantly correlated with birth weight. Other neonatal morbidities, however, are unrelated to either maternal age or obesity but correlate to some degree with severity of maternal DM, as reflected by glycemic control.

Contemporary efforts to maintain normoglycemia during pregnancy with diet, exercise, and aggressive insulin therapy may result in normalization of glycated hemoglobin and near-normal glucose profiles throughout the day by self-monitoring of blood glucose concentrations. Despite this degree of near-normalization of glycemia, however, neonatal morbidities persist (16) (Table 89-4). Controlling blood sugars using postprandial glucose monitoring goals (1 hour postprandial <140 mg/dL) in combination with fasting blood glucose measurement (fasting 60 to 90 mg/dL) can optimize glycemic control and significantly improves pregnancy outcomes by decreasing neonatal hypoglycemia and macrosomia, and the rate of cesarean sections (81).

TABLE 89-4. Neonatal complications in infants of mothers with gestational diabetes mellitus

Complication	GDM (n = 878)	Control (n = 380)	Relative risk
Macrosomia	17.9%[a]	5.6%	3.2[a]
Hypoglycemia	5.1%[a]	0.9%	5.7[a]
Hyperbilirubinemia	16.5%[a]	8.2%	2.0[a]
Hypocalcemia	5.5%[a]	2.7%	2.0[a]
Polycythemia	13.3%[a]	4.9%	2.7[a]
Thrombocytopenia	0.6%	0.9%	0.7
Hyaline membrane disease	1.3%	1.4%	0.9
Major anomalies	3.0%[a]	1.8%	1.7[a]

GDM, gestational diabetes mellitus.
[a]$p < .05$.
Adapted with permission from Hod M, Merlob P, Friedman S, et al. Gestational diabetes mellitus: a survey of perinatal complications in the 1980's. *Diabetes* 1991;40[Suppl 2]:74.

The *in utero* exposure to abnormal metabolic parameters has long-term consequences in addition to the short-term consequences seen in the perinatal period. Offspring of women with GDM are heavier for gestational age and heavier for height than offspring of nondiabetic women matched for age and BMI (82). This neonatal obesity creates a problem that these children are apparently unable to overcome. As they age, within each age group, the offspring of diabetic women have a higher prevalence of obesity than their matched cohort. Similarly, these offspring have higher glucose concentrations in response to glucose tolerance tests and a higher prevalence of DM than their matched cohort. This study is particularly interesting in that the infants of women with GDM continued to have a significantly greater incidence of obesity and DM even when matched with infants of women with normal carbohydrate tolerance during the index pregnancy who subsequently acquired type 2 DM. Thus, the effects of the intrauterine environment may be separated from the effects of heredity, and can be demonstrated to have lasting effects on the anthropomorphic and metabolic development of the offspring (82).

CONCLUSION

Discriminating the effects of maternal age, obesity, and degree of maternal glycemic control has complicated the assessment of fetal effects of GDM. Use of NDDG criteria for the diagnosis of GDM and differing thresholds for the initiation of insulin therapy, with resulting differences in maternal glycemic control, complicate our understanding of the impact of GDM on the fetus. Standardization of diagnostic criteria and therapeutic interventions, together with intensive examination of fetal and maternal metabolic parameters, will contribute significantly to our understanding of the impact of GDM. Nonetheless, GDM serves as an ideal model for examining the natural history of type 2 DM and the effects of early intervention for prevention. Furthermore, infants of mothers with GDM provide a model for the effects of early nutrition, as well as an opportunity to reduce the occurrence of neonatal morbidities. New efforts are underway to improve ascertainment of GDM, measurement of metabolic parameters, and examination of fetal outcomes in a controlled fashion (83).

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